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Review

Animal models of attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) involves clinically heterogeneous dysfunctions of sustained attention, with behavioral overactivity and impulsivity, of juvenile onset. Experimental models, in addition to mimicking syndromal features, should resemble the clinical condition in pathophysiology, and predict potential new treatments. One of the most extensively evaluated animal models of ADHD is the spontaneously hypertensive rat. Other models include additional genetic variants (dopamine transporter gene knock-out mouse, coloboma mouse, Naples hyperexcitable rat, acallosal mouse, hyposexual rat, and population-extreme rodents), neonatal lesioning of dopamine neurons with 6-hydroxydopamine, and exposure to other neurotoxins or hippocampal irradiation. None is fully comparable to clinical ADHD. The pathophysiology involved varies, including both deficient and excessive dopaminergic functioning, and probable involvement of other monoamine neurotransmitters. Improved models as well as further testing of their ability to predict treatment responses are required.

Theme: Neural basis of behavior

Topic: Monoamines and behavior

Keywords: Attention deficit-hyperactivity disorder; Behavior; Dopamine; Hyperactivity; Norepinephrine; Serotonin; Stimulants

Contents

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1. Introduction

1.1. General aspects of animal models of ADHD

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous neuropsychiatric syndrome of inattention, hyperactivity, and impulsivity, typically of juvenile onset [20]. Although its etiology remains unknown, modern research methods, including molecular genetics and brain imaging, have greatly expanded knowledge about this relatively common disorder. Recent advances in the study of clinical ADHD are summarized in several authoritative reviews [19,33,38,51,197,251, 253,272].

For decades, basic research related to ADHD has been supported by animal models representing specific components of the clinical condition, and used to advance knowledge of the pathophysiology and therapeutics of ADHD. Animal models of ADHD include several genetic mutants, either naturally occurring or artificially produced, as well as animals prepared by brain lesioning or exposure to neurotoxins, typically early in development [89,193, 227,254]. With relatively homogeneous subjects, these models allow considerable experimental control of factors that may be involved in the pathophysiology of ADHD. They also avoid complex effects of comorbidity, previous drug exposure, family interactions, and other social factors encountered in human ADHD patients.

In general, animal models should resemble a clinical disorder in as many details as possible, including symptomatic expression, treatment responses, pathophysiology, and ideally, etiology. More specifically, an adequate ADHD model should: (a) mimic the fundamental behavioral deficits found in ADHD patients (*face validity*); (b) conform to a theoretical rationale, such as the proposed pathophysiology or known therapeutics of ADHD (*construct validity*); and (c) predict unknown aspects of ADHD, such as its genetics, neurobiology, or novel therapeutics (*predictive validity*). This review considers conditions in laboratory animals that have been used as experimental models for ADHD in the context of these criteria. Construct validity is particularly important in view of a number of recent advances in understanding the genetics and pathophysiology of ADHD.

1.2. Clinical features and biology of ADHD

1.2.1. Clinical features

ADHD is a heterogeneous syndrome that includes fundamental behavioral and cognitive features, notably, inattention, impulsivity, and variable hyperactivity [4,20]. It is diagnosed in both males and females and is typically associated with poor academic performance, though it is more often recognized in boys due to their typically overactive or disruptive behavior [4,20,101]. No clinical feature or testing procedure is specific for ADHD [4], and diagnosis is based on clinical assessment of behavior supplemented with psychological and neurocognitive evaluation.

A particularly troublesome problem is that measures of specific features of ADHD correlate inconsistently and vary substantially among individuals [18,22,216,279]. As a result, debate continues about the clinical limits of the diagnosis, and even about the basic validity of ADHD as a discrete disorder [144,239]. Social critics charge that professionals are too quick to label 'normally' energetic and exuberant children as having a 'disorder', use the label to excuse failed educational efforts, overuse stimulant treatment inappropriately, and risk stigmatization of children as mentally ill or neurologically impaired. Despite uncertainties in individual cases and some potential for abuse of the diagnosis and treatment, differences between children diagnosed as typical cases of ADHD and their peers are sufficient to sustain a clinically useful diagnostic core concept [150]. Moreover, without intervention, risks of dysfunction, disability or social impairment await many children meeting diagnostic criteria [19,20].

The apparent lack of coherence of ADHD symptoms,

and limited robustness of the diagnosis, may reflect limited measurement reliability, overemphasis on hyperactivity, and insufficient consideration of cognitive dysfunctions [18,268]. Alternatively, clinical complexity may reflect a heterogeneous pathophysiology, and environmental processes can modify specific components of brain function at distinct developmental periods to yield highly variable clinical presentations [19,33,51,85,187,192].

1.2.2. Pathophysiological hypotheses

A widely accepted hypothesis is that ADHD represents dysfunction of the prefrontal cerebral cortex of unknown cause [8,85,230]. Supporting evidence for this hypothesis includes similarities of clinical features of ADHD patients and those with injuries or diseases of the frontal lobes, as well as ADHD-like behavioral and neurocognitive deficits in animals with lesions of frontal cortex [7,9,21,27,57, 72,129,168,244,292,295]. At a molecular level, the striking and consistent beneficial clinical effects of stimulant drugs in patients with ADHD, and evidence that such drugs facilitate monoaminergic synaptic neurotransmission, particularly of dopamine (DA), have strongly encouraged speculation that aberrant, and particularly deficient, cerebral monoamine neurotransmission may contribute to the pathophysiology of ADHD [17,89,197,235]. However, the hypothesis that ADHD is associated with deficient DA transmission has limited and inconsistent direct experimental support by clinical metabolic studies and findings of brain-imaging studies considered below.

Some support for a role of DA in the pathophysiology, and especially the therapy, of ADHD comes from studies of DA and its metabolites in the body fluids of ADHD patients [52,53]. Notably (and probably circularly) hyperactive behavior and superior responses to stimulant treatment in ADHD patients have been associated with elevated cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA), a principal metabolite of DA. Additional complex findings that are not readily interpreted derive from use of computed positron emission tomography (PET) of the brain. This functional imaging technique has demonstrated *increased* uptake of the labeled DA precursor [^{18}F]-L-dopa in the midbrain of some adolescents with ADHD [83], but *decreased* uptake in the prefrontal cortex (PFC) of adult ADHD patients [82]. Additional functional brain-imaging studies comparing ADHD patients and normal controls have labeled the DA transporter (DAT) protein, a specific marker for DA neurons, with nonhydrolyzable phenyltropane analogs of cocaine. These DAT radioligands include [^{131}I]altropane [75] for PET, and [^{99m}Tc]TRODAT-1 and [^{131}I]β-CIT for single photon emission computed tomography (SPECT) [75,76,146,281]. All but one study involving these radioligands [281] found *increased* binding to DAT in the DA-rich basal ganglia of ADHD subjects. However, again, the correct interpretation of these observations is far from clear. They may reflect increased abundance or tissue density of DA nerve terminals, or an increase in DAT-per-neuron, perhaps with a net reduction of synaptic availability of DA, and artifacts due to previous treatment are not entirely excluded. In addition, improvement in clinical symptoms with d,l-methylphenidate was associated with decreased DAT binding [76,146]. This effect evidently reflects the ability of this stimulant, and perhaps released DA, to compete for DAT binding sites with the radioligands employed, and not necessarily evidence that stimulants alleviate ADHD symptoms by correcting an underlying abnormality in DA neurotransmission.

A role of norepinephrine (NE) in ADHD is suggested by the effectiveness of tricyclic and other antidepressant drugs that are selective inhibitors of the NE-transporter (NET) [32,33,198], as well as α_2-adrenergic agonists [127,128, 231], in alleviating clinical symptoms of the disorder. A role of serotonin (5-hydroxytryptamine; 5-HT) neurotransmission in clinical ADHD is less secure since serotonin-selective reuptake inhibitors (SRIs) have limited benefit in ADHD patients [20,26,51,198]. Nevertheless, 5-HT is implicated in both the pathophysiology and pharmacology of several ADHD models reviewed below.

1.2.3. Genetic hypotheses

ADHD has been linked to polymorphisms of several genes implicated in monoamine neurotransmission [194,275], including the DA transporter (DAT1) [63] and D_4 receptor (DRD4) genes [151]. ADHD was associated with polymorphism of DAT1 in some studies [63,105,266], but not others [214,276], and the associated alleles may be particularly effective in transporting DA into nerve terminals [95,113,164,171,175].

The D_4 receptor gene (DRD4) is located in the short (p) arm of human chromosome 11, at position 11p15.5 [282]. The greatest variance in peptide sequence from other DA receptors occurs in the third intracellular sequence of this peptide, which is required for interaction with G proteins and second-messenger signaling [282]. An association between ADHD and a relatively long, 7-repeat allele (DRD4.7), involving a repeating 48 base-pair (16-amino acid) sequence that affects the length of the third intracellular loop, was first identified by La Hoste and colleagues in 1996 [151]. This linkage has been confirmed by most [23,86,247,269], but not all, later studies [78,111,277], and meta-analysis of these results supported a significant but modest association with ADHD [87]. The same $D_{4.7}$ genotype was also associated with personality traits related to ADHD, including novelty-seeking and impulsivity [29,77]. The $D_{4.7}$ receptor is considered less sensitive to DA and less efficient than other forms of D_4 receptor in transducing DA-stimulated intracellular signals, such as inhibition of adenylyl cyclase [13]. Such findings encourage speculation that beneficial effects of stimulants may include indirect activation of hypofunctional cerebral D_4 receptors in ADHD patients.

Candidate genes of the NE neurotransmission system also have been considered in ADHD [33,301,302]. Barr and colleagues [25,299] tested genes encoding two α-adrenoceptors, α_{1C} (ADRA1C; located in the short arm of human chromosome 8, at 8p11.2) and α_{2C} (ADRA2C; at 4p16). With transmission dysequilibrium analysis, they found no biased transmission of any known allele of these genes, and concluded that the alleles considered were not linked to ADHD in the families tested.

Encouraged by findings that nicotinic acetylcholine (ACh) receptor agonists can improve attention, learning, and memory in ADHD patients [153,286,291], the α_4 nicotinic receptor gene (CHRNA4) was studied in 70 family samples involving children with ADHD, with no evidence of an association with ADHD [141].

1.2.4. Neurodevelopmental hypotheses

Studies of obstetrical complications as contributing factors for ADHD have yielded conflicting results. Compared to normal controls, children with ADHD were found to have had a higher incidence of perinatal hypoxia [159,259]. However, associations of ADHD with other perinatal complications, including toxemia, older maternal age, and premature birth, have been inconsistent and remain inconclusive [303].

A developmental defect leading to anomalous symmetry or interhemispheric connectivity of the brain has also been considered in ADHD [92,100]. Reduced size of the corpus callosum, particularly in its rostral or splenial portion, has been detected in some children diagnosed with ADHD [28,163], and the typically larger corpus callosum in the human female brain [125,134] may be protective against ADHD [6,101]. However, a direct link between ADHD and defective transfer of information between the cerebral hemispheres has not been demonstrated in ADHD. Moreover, substantial callosal hypoplasia usually is associated with other major neurodevelopmental disorders that are not specifically associated with ADHD [294].

Recently, the cerebellum has been implicated in cognition and emotion, in addition to its traditional role in coordinating movement and maintaining body posture during ambulation [91,152], suggesting a possible contribution to ADHD that is consistent with reports of deficits in fine motor control in some ADHD patients [31,110,289]. As the primary site for memory consolidation, the hippocampal formation is also of potential interest in ADHD. Structural brain imaging has not revealed evidence of structural abnormality of the hippocampus [54,92], but functional imaging has found reduced cerebral glucose metabolism in this brain region in adolescent girls with ADHD [80,81].

1.2.5. Toxicological hypotheses

Studies of hypothesized dietary factors, including excessive ingestion of sucrose, have yielded mainly negative results, but other environmental toxins have been implicated in ADHD. Lead exposure during development can produce various nonspecific neurobehavioral abnormalities, including hyperactivity, restlessness, distractibility, and impaired cognition. However, lead contamination is not found in most cases of ADHD [185,186]. Parents of ADHD children may consume more alcohol and tobacco than parents of normal controls [65], and exposure to alcohol or tobacco smoke during early development may be a risk factor for ADHD [173,263,264].

2. Laboratory models of ADHD

2.1. Genetic models

2.1.1. Spontaneously hypertensive rat

In the early 1960s, the spontaneously hypertensive rat (SHR) was developed in Japan by inbreeding rats of the Wistar-Kyoto (WKY) strain [188]. Selecting for hypertension also yielded unexpectedly high spontaneous motor activity [179]. Over several decades, Sagvolden and colleagues [227–229] at the University of Oslo studied the SHR extensively and established it as one of the most widely used animal models of ADHD.

SHR shows several features characteristic of ADHD [179,227], including motor hyperactivity in a novel environment, excessive responses under a fixed-interval/extinction schedule, and difficulty in acquiring operant tasks [178,227,297,298]. These behavioral abnormalities correspond to the clinical features of hyperactivity, impulsivity, and learning deficit, respectively. Hyperactivity and impulsivity in SHR was attenuated by agents that potentiate monoaminergic neurotransmission, including amphetamine and the monoamine oxidase (MAO) inhibitor selegiline ([−]-deprenyl) [36,182]. Also similar to patients with ADHD [228], the SHR is more sensitive to immediate behavioral reinforcement and less sensitive to delayed reinforcement than are nonhypertensive WKY control rats [229]. These similarities strongly support the face validity of the SHR as an animal model for ADHD. However, other features are discordant, notably, a lack of sex-differences in SHR [30].

The behavioral and cognitive abnormalities in SHR are also responsive to stimulants, including d-amphetamine and d,l-methylphenidate [182,229], adding to the construct validity of SHR as a model of ADHD. In a two-compartment test setting with a home area freely accessible to a contiguous open field, SHR spent most of test sessions in the open field, whereas normal WKY rats preferred the home area [298]. Low to medium doses of methylphenidate moderately increased activity of SHR, but induced intense motor hyperactivity in WKY rats. At high doses, methylphenidate reduced locomotion and rearing in both SHR and controls, apparently due to emergence of stereotyped behavior [298]. Similar to their clinical effects in ADHD, stimulants weakened the influence of immediate

reinforcers on behavior, and strengthened that provided by delayed reinforcers, although these effects were less pronounced in SHR than in WKY controls [229].

Blunted responses of SHR to stimulants seem to be mediated by impaired release of DA from nerve terminals in prefrontal cerebral cortex (PFC), nucleus accumbens, and caudate-putamen [72,139,183,217,219–221]. In addition, metabolic turnover of DA (indicated by the ratio of its metabolites to DA) in the neostriatum (bilateral) and nucleus accumbens (right side only) of SHR was less than in control WKY rats [36]. Amphetamine increased release of DA more than methylphenidate in SHR brain tissue, presumably reflecting its greater effect on intraneuronal vesicular storage, in addition to effects on DA reuptake of both agents [220]. This finding may suggest an abnormality in vesicular storage of DA in SHR.

In addition to abnormal presynaptic DA transmission, molecular indices of postsynaptic neurotransmission in brain, including activity of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and expression of the immediate early genes *c-fos* and *zif*-268 also were lower in SHR than in normal WKY rats [191,223]. Interestingly, CaMKII levels normalized with repeated daily treatment of SHR with methylphenidate [191]. Young, pre-hypertensive, male SHRs had *increased* tissue concentrations of D_1 or D_5 receptors in rostral neostriatum, accumbens, and olfactory tubercle, presumably secondary to deficient stimulation by DA. The receptor changes normalized with repeated methylphenidate treatment [48]. These findings are consistent with the view that stimulants alleviate ADHD symptoms by correcting deficient dopaminergic neurotransmission.

Increased NE transmission also has been detected in the SHR. NE uptake by synaptosomal preparations of cerebral tissue of SHR was *greater* than in WKY rats in all brain areas tested [183], suggesting decreased noradrenergic function. Increase NE reuptake was not a direct result of high blood pressure since it was found before hypertension emerged. However, in the PFC, NE release in response to glutamate was increased in comparison to control WKY rats [222]. Inhibition of NE release by the α_2 autoreceptor may also be deficient in SHR [218], leading to overall *increased* NE transmission, and presumably affecting blood pressure as well as behavior. Indeed, hypertension is a potential confounding factor for SHR as a model for ADHD. Many behavioral deficits in SHR, especially those related to learning and memory, might reflect brain dysfunction or damage caused by high blood pressure. Also, whether beneficial effects of drugs such as the α_2-adrenergic agonists clonidine and guanfacine in this model as well as in clinical ADHD, reflect direct central neuropharmacological effects of these agents, or lowered blood pressure, remains uncertain [89,227,298].

In an effort to separate hyperactivity from hypertension, Hendley and her colleagues at the University of Vermont selectively bred hypertensive-only (WKHT) and hyperactive-only rats (WKHA) by crossbreeding SHR with WKY rats [114–116]. In WKHA rats, prominent behaviors include hyperactivity in a novel environment and increased reactivity to stress, both of which are also characteristic of SHR [114–116]. However, WKHA rats are less aggressive than classic SHR, and habituate more readily to a novel environment [114,116]. In addition, the uptake of DA in WKHA brain tissue was significantly greater than in the hypertensive strains (WKHT and SHR) [115], tending to implicate altered DA transmission in the trait of hyperactivity rather than in hypertension. In contrast, increased neuronal uptake of NE, which was specific to SHR and WKHT strains only, and was not found the hyperactive WKHA rats [115], suggesting that altered NE neurotransmission may contribute to hypertension rather than hyperactivity.

2.1.2. Dopamine transporter knockout mouse

The neuronal reuptake process mediated by neuron-specific monoamine transporter proteins in neuronal membranes is the primary mechanism for close control over synaptic signaling by monoamine neurotransmitters [93,98]. Stimulants inhibit or reverse the functioning of the DA transporter (DAT), and exert additional effects on NE (NET) and 5-HT transporters (SERT), as well as variable effects on presynaptic vesicular uptake and storage processes [147,148]. Increased DA transmission in the basal ganglia and limbic forebrain is believed to underlie behavioral activation induced by stimulants [56]. Genetically engineered 'knockout' (*DAT-KO* or $DAT^{-/-}$) mice lack functional DAT and demonstrate striking spontaneous behavioral hyperactivity compared to wild-type ($DAT^{+/+}$) mice during both light and dark phases of the daily cycle [97,99,106]. The half-life of behavioral habituation in homozygous $DAT^{-/-}$ mice was over twice that of heterozygous ($DAT^{+/-}$) littermates (90 vs. 40 min), and much longer than in wild-type mice. DAT-KO mice also showed significant cognitive impairment in an eight-arm radial maze, a standard test of spatial learning [97,99]. Further behavioral analysis demonstrated no apparent deficits in social behavior [258].

Robust behavioral hyperactivity in DAT-KO mice was associated with an approximately 300-fold decrease in the rate of clearance of extracellular DA, as measured by cyclic voltammetry in brain striatal slices [137]. Profound, evidently compensatory, changes also occur. They include decreases in tissue content (by 95%) and release of DA (by 75%) from nerve terminals [98,137]. As a result, extracellular DA concentration was increased only by 5-fold despite complete loss of DAT in homozygous DAT-KO mice. DA metabolites have, variably, been either increased (HVA), or unaltered (3,4-dihydroxyphenylacetic acid [DOPAC]) in the DAT-KO mouse [137]. Synthesis of DA (at the rate-limiting step of L-tyrosine hydroxylation) was increased as measured by accumulation of L-dopa follow-

ing inhibition of L-aromatic amino acid decarboxylase, apparently due to allosteric modulation of tyrosine hydroxylase (TH) activity [130,131,137]. Increased TH activity is thought to reflect loss of tonic inhibition of TH by DA in nerve terminals, as well as an unexplained loss of negative feedback control of TH activity by presynaptic D_2 autoreceptors that may involve dysregulated activation of TH by phosphorylation [106,136]. Despite these profound functional alterations at DA terminals, anatomical abnormalities of DA neurons have not been found, even at the electron-microscopic level [97,98,106].

In addition to adaptive presynaptic changes in DA neurons, postsynaptic D_1 and D_2 receptors were also significantly down-regulated in DAT-KO mice, with approximately 50% decreases in both their mRNA and protein levels in basal ganglia [98,130,131]. These changes are quantitatively unprecedented, and seem to be directed toward restoring functional homeostasis of dopaminergic neurotransmission disturbed by loss of DAT [136,137]. Levels of the mRNA for preproenkephalin-A (possibly under inhibitory control by D_2 receptors) was substantially reduced, whereas the message for dynorphin (responsive to stimulation by D_1 receptors) significantly increased [106].

Behavioral hyperactivity in DAT-KO mice can be inhibited by amphetamine, methylphenidate, and cocaine [97,98,138]. Since DAT is a primary molecular target of stimulant drugs, these findings seem counter-intuitive. Also *inconsistent* with the view that behavioral effects of stimulants are mediated primarily by DA neurotransmission is the finding that DA concentrations in neostriatum of DAT-KO mice did not increase with challenges with these drugs or with environmental novelty [97–99], although a relatively intact DA system seemed necessary for the behavioral effects of stimulants [99]. 5-HT seemed to be a prime candidate for such pharmacological effects since the motor hyperactivity in DAT-KO mice was also antagonized by the 5-HT releasing agent fenfluramine, the SRI antidepressant fluoxetine, and the 5-HT agonist quipazine [99]. Moreover, pharmacological depletion of 5-HT abolished the antihyperactivity action of fenfluramine. NE also may be involved since behavioral responses to amphetamine and cocaine were mimicked by selective inhibitors of NET but not of DAT [45].

DAT-KO mice also show other abnormalities not found in ADHD, including growth retardation and premature death. By 10 weeks of age, survival is only about 68% in homozygotes vs. 97% in wild-type controls [98,106]. DAT-KO mice can reproduce, but females show impaired maternal behavior, and their young require cross-fostering by normal dams to survive [37,98]. Changes in reproductive behavior are paralleled by loss of prolactin-producing cells in the anterior pituitary, and depressed functioning of the hypothalamus [37,96].

2.1.3. Coloboma mutant mouse

The coloboma mutant mouse was produced by neutron irradiation, and only the heterozygote ($Cm^{+/-}$) is viable [234]. $Cm^{+/-}$ mouse shows a variety of behavioral deficits that resemble core features of ADHD, including pronounced spontaneous motor hyperactivity, and delayed neurodevelopmental milestones [117,119,121,293]. On average, these mutants are three-times more active than normal controls, with considerable individual variation [118,119,121]. Hyperactivity in coloboma $Cm^{+/-}$ mouse was reduced by low doses of d-amphetamine (2–4 mg/kg). In contrast, methylphenidate (2–32 mg/kg) *increased* locomotor activity in both the mutants and normal controls in a dose-dependent manner [118].

Behavioral changes in coloboma mouse are associated with a mutation of the gene encoding SNAP-25, a synaptosome-associated protein of 25 kDa molecular mass [118,119,262]. As a key component of the synaptic vesicle-docking-and-fusion process that is essential for exocytotic release of catecholamines and other neurotransmitters, SNAP-25 forms a stable ternary complex with the synaptic proteins syntaxin-1a and VAMP-2 (synaptobrevin-2). Mutation of SNAP-25 leads to profound disruption of dopaminergic neurotransmission. DA release induced by neuronal depolarization is almost completely lost in the dorsal, but not ventral, striatum of this mouse, and somewhat augmented in its cerebral cortex [203]. These regionally selective functional deficits in DA release may underlie the behavioral hyperactivity observed in this mutant, and changes in hippocampal physiology may contribute to impaired information processing also found in this model [293]. In addition to changes in DA systems, increased concentrations of NE also were found in striatum and nucleus accumbens of the coloboma mutant [135].

In an effort to identify a possible contribution of SNAP-25 in human ADHD, Hess and colleagues examined polymorphic markers in the region of chromosome 20 syntenic to coloboma (20p11–12) in five human pedigrees, in which inheritance of ADHD appeared to be best explained by a sex-influenced, single-gene, Mendelian model [120]. They found no linkage between the disease and markers near the SNAP-25 gene locus. Another clinical genetic study used single-stranded conformational polymorphism-analysis (SSCP) to determine DNA sequences in the 3′-untranslated region of the human SNAP-25 gene [24]. Two polymorphisms were identified in this region by use of restriction enzymes. Transmission of the alleles for each polymorphism and their haplotypes were examined by transmission dysequilibrium in 97 families of ADHD probands, their parents and siblings. Biased transmission of the haplotypes of the alleles of both polymorphisms was found, suggesting a role of the SNAP-25 gene in ADHD.

2.1.4. Naples high-excitability rat

Naples high-excitability (NHE) rat is another genetic animal model of ADHD that may involve excessive DA functioning in limbic and cortical areas of forebrain

[14,108,190,191,224,225]. The NHE strain is hyperexcitable and shows deficits in tasks requiring visuospatial attention [14,191]. The high reactivity of NHE rats to novelty is not based on generalized hyperactivity, since their 24-h spontaneous motor activity did not differ significantly from that of random-bred controls (NRB), or a low-excitability (NLE) strain. Responses of NHE rats to stimulants remain to be evaluated fully.

Based on immunocytochemical analysis, NHE rats, compared to NRB controls, had larger DA neurons and higher TH content in the ventral tegmental area (with cell bodies of the mesolimbic DA system), but not in substantia nigra (origin of the nigrostriatal DA system) [224,283]. These findings suggest that increased behavioral activity and impaired attention of NHE rats may be associated with hyperfunctioning of the mesocorticolimbic DA system.

2.1.5. Acallosal mouse strain I/LnJ

The inbred acallosal mouse strain I/LnJ shows total callosal agenesis with complete penetrance, with behavioral features resembling ADHD, including impaired acquisition in conditioned learning tasks [156,157,165]. Among mice produced by crossing I/LnJ with normal wild-type C57BL/6 mice, those with ≥88% of alleles of the I/LnJ strain were hyperactive in an open field, with considerable individual variability [165]. Acallosal mouse also showed fewer brief stops and spent more time in the center of the open field at the beginning of the session. Time spent in the center of an open field was associated with lower uptake of radiolabeled 2-deoxyglucose in left striatum and cerebral cortex, whereas brief stops correlated with bilaterally lower metabolic activity in frontal and parietal cortex [165]. These observations suggest that behavioral hyperactivity in this callosal agenesis model is related to functional dominance of the right hemisphere that may be exaggerated by the lack of callosal connections. Interestingly, specific dysfunction of the right cerebral hemisphere is also suggested to occur in clinical ADHD [100,261], although there is no evidence of either malformation or dysfunction of the corpus callosum in brains of ADHD patients.

The relationship of callosal agenesis to behavioral disinhibition in the acallosal mutant mouse may be further clarified by comparing behavior in mice with variably sized corpora callosa, as well as with acallosal animals with different genetic backgrounds [285]. Status of neurotransmitter function and effects of stimulants remain to be tested in acallosal mice as a potential animal model of ADHD.

2.2. Neurotoxin-exposed animals

2.2.1. Juvenile rats with neonatal 6-hydroxydopamine brain lesions

Extensive lesioning of DA neurons in adult animals results in behavioral deficits characteristic of Parkinson's disease, including bradykinesia, sensory neglect, aphagia and adipsia [166,280,308]. In contrast, selective removal of DA projections to forebrain in neonatal rats leads to age-limited spontaneous motor hyperactivity [64,112,160, 162,242,243], without gross deficits in sensorimotor function [44,248,287]. Hyperactivity in the model is most prominent at an age corresponding to human periadolescence [79,243,307], and is dose-dependently antagonized by stimulants [67,112,162,242]. As a result, juvenile rats with neonatal DA lesions are widely used to model ADHD and its treatment.

Neonatal DA lesioning also results in loss of sensitivity to the intoxicating effects of ethanol and diazepam [84]. These findings may have clinical relevance since ADHD is a risk factor for alcohol abuse and antisocial behaviors [19,20,110]. In addition, the neonatally lesioned rat shows deficits in learning and memory, as suggested by impaired acquisition of spatial discrimination tasks and operant responses [5,241,271,288]. Learning deficits can be detected as early as 48 h after neurotoxin treatment, reach maximal levels soon after weaning, and typically disappear by adulthood. Similar to responses of motor behavior to stimulants, learning deficits induced by neonatal DA lesions also respond favorably to stimulant treatment. Thus, deficits in conditioned learning based on olfactory cues in these rats were alleviated by amphetamine [296], and T-maze learning was improved by methylphenidate [241].

Sparing of sensorimotor functions after neonatal DA lesioning, and the age-limited behavioral deficits that follow such lesioning, may reflect ability of young animals to repair or regenerate DA neurons after insults. Late, unilateral lesioning of the nigrostriatal DA projection in adult rats following neonatal lesioning with 6-OHDA produced contralateral sensorimotor deficits, suggesting that regeneration of DA neurons may be sufficient to restore motor functions in adult rats with neonatal lesions [208]. Adaptive functional changes in the remaining DA neurons are also indicated by increased DA release from terminals [46,50], and increased TH mRNA and protein levels in cell bodies [34,140]. Compensatory mechanisms tending to restore DA transmission also include loss of presynaptic D_2 autoreceptors that normally inhibit the firing of these neurons, and of DAT that normally removes DA from the synaptic cleft [140,232].

In addition to presynaptic changes in DA transmission, postsynaptic mechanisms are also altered after neonatal DA lesions. Sensitivity of D_1 receptors to agonists is increased, with decreased response to D_1 antagonists. Altered D_1 receptor sensitivity is strongly implicated in L-dopa-induced self-injurious behavior in neonatally lesioned rats [39–42]. In contrast, neonatally lesioned rats are less sensitive to D_2 antagonists such haloperidol, whereas rats lesioned with 6-OHDA in adulthood are exquisitely sensitive to such drugs, again suggesting that adaptive responses of DA receptors to loss of DA during

early development are fundamentally different from those induced by DA lesions in adulthood [140].

Loss of DA during early development also leads to profound adaptations in the 5-HT system. These include substantial, regionally-selective, and sustained 5-HT hyperinnervation of striatum [71,94,145,161,260,278,305]. Quantitative immunocytochemistry revealed increased tissue content of 5-HT associated with proliferation of 5-HT nerve terminals [278]. However, the functional significance of 5-HT hyperinnervation of the striatum remains unclear. The increase of 5-HT fibers after lesioning did not interfere with outgrowth of DA-containing fibers arising from transplanted DA cells, nor did such transplantation in neonatal brain prevent 5-HT hyperinnervation after 6-OHDA lesioning [250]. Another important finding is that rats with early lesions to *both* DA and 5-HT systems (produced with 6-OHDA plus 5,7-dihydroxytryptamine) did not exhibit symptoms characteristic of Parkinson's disease [44], suggesting that 5-HT does not compensate for the loss of DA to maintain motor functions. Furthermore, hyperinnervation by 5-HT in striatum did not occur if 6-OHDA lesions were carried out at later ages (e.g. at postnatal days [PD] 15–27), yet such preweaning and adolescent-lesioned rats were devoid of major motor deficits [140].

In contrast to adaptive changes in the 5-HT system, development of the central NE system seems to be normal in rats with neonatal 6-OHDA lesions [161,189]. Moreover, an intact NE system is necessary for the antihyperactivity effects of stimulants that potentiate the release NE as well as DA [147,148]. Indeed, amphetamines, including d-amphetamine, d-methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA), release NE more potently than DA [215]. Moreover, the calming effects of stimulants can be mimicked by selective inhibitors of NET such as desipramine and nisoxetine, but not by selective inhibitors of DAT such as GBR-12909 and amfonelic acid [68]. These findings parallel compelling evidence of clinical benefits in ADHD of selective inhibitors of NET including desipramine, nortriptyline, and atomoxetine [32,33,198,257]. Mechanisms by which inhibitors of NET alleviate hyperactivity remain unknown, but they may include α-adrenergic enhancement of prefrontal cerebral cortical functioning [10–12,16,158].

The well-established normalization of motor hyperactivity as neonatally lesioned rats reach adulthood is particularly intriguing. Re-innervation of the neostriatum by DA-rich cell transplants limits hyperactivity [46,47]. Normalization of motor behavior in neonatally 6-OHDA-lesioned rats correlated with gradual recovery of DA innervation in nucleus accumbens, but not caudate-putamen [307], as quantified by transporter autoradiography using a selective DA transporter radioligand [149].

D_4 receptor plasticity also may contribute to behavioral hyperactivity in this model. First, motor hyperactivity in neonatally 6-OHDA-lesioned rats correlated with substantial increases in levels of D_4, but not other DA receptors, in caudate-putamen [306]. Second, lesion-induced motor hyperactivity was dose-dependently inhibited by several D_4 receptor-selective antagonists, but not by D_2/D_3 antagonists [304,306]. Third, increased D_4 receptor binding in forebrain tissue of lesioned rats was detected only in early development when hyperactive behavior was pronounced, but not later when motor activity returned to control levels [307]. Since D_4 receptor polymorphism has been repeatedly linked to ADHD (see Section 1.2.3.), these findings strongly suggest that abnormal development of the D_4 receptor might contribute to hyperactivity in ADHD patients and that D_4-selective antagonists may represent a much needed, novel treatment for ADHD.

2.2.2. Neonatal hypoxia in rats

In rats, cerebral hypoxia induced by 25 min of immersion in 100% nitrogen at 30 h after birth leads to behavioral abnormalities with some similarities to ADHD [70,255,256]. These include age-limited hyperactivity in an open field that is most prominent at PD 20–45, and permanent deficits in learning and memory [109]. Treatment with d-amphetamine can counteract the hyperactivity, but stimulants have not been adequately tested for effects on learning and memory in this model [256].

Neonatal hypoxia results in complex alterations in the central monoamine systems that change with age [70]. Initially, at 20 min post-anoxia, levels of NE in cerebral cortex, DA in striatum, and levels of their metabolites were reduced, whereas tissue concentrations of the principal 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were increased in cerebral cortex and cerebellum [70]. In contrast, 1 week later, NE was increased in cerebellum, and both 5-HT and 5-HIAA levels were decreased in cortex and cerebellum. By PD 21, hippocampal NE and striatal HVA levels were increased, striatal 5-HT decreased, with increased 5-HIAA in both striatum and hippocampus, and at PD 60, striatal levels of DOPAC and 5-HIAA were increased [70]. Possible relationships of these complex metabolic changes to the neurobehavioral manifestations in the model, let alone to the pathophysiology of clinical ADHD, remain to be investigated.

Neonatal hypoxia in rats also produces long-lasting morphological change in hippocampus [69]. Neuronal density was reduced selectively in CA1 at PD 15 and later, but an index of neural repair, fibrillary staining in astroglia, increased as early as PD 7 [69]. The number of neurons showing immunoreactivity for the immediate early gene *c-fos* was also decreased in hippocampal CA_1, CA_2, and CA_3 regions [69]. These findings suggest that hippocampal damage may contribute to deficits in learning and memory typical of neonatally hypoxic rats.

2.2.3. Developmental cerebellar stunting in rats

Neuroanatomical and functional effects of insults to the immature cerebellum vary with age and the state of neural

development. Very early surgical lesions of the cerebellum or exposure to toxins at PD 1–4 produce severe changes in cerebellar morphology, with ataxia and tremor, and generally reduced activity with poorly coordinated movements, as well as some deficits in learning and memory. Similar insults only a few days later (PD 5–12) cause less severe neuropathology, with motor hyperactivity and minor learning deficits that simulate ADHD [88–90].

The antimitotic agent methylazoxymethanol acetate, given to rats at PD 5–8, permanently reduced cerebellar weight with relatively minor effects in other brain regions [88,90]. This treatment produced mild hyperactivity in open field and running-wheel tests that was more pronounced in males, without gross deficits in learning tasks. Also, treatment of rats with the synthetic glucocorticoid dexamethasone during early development caused permanent reduction in cerebellar weight and mild behavioral hyperactivity, again mainly in male rats, without gross learning deficits [89]. Finally, oral administration of all-*trans*-retinoic acid to pregnant rats resulted in decreased cerebellar weight and hyperactivity in a running wheel test in their offspring [126].

These observations suggest that some features of ADHD can be simulated by early cerebellar damage in the rat. However, more detailed analyses of behavioral consequences of such damage and effects of stimulants are needed to establish animals with early cerebellar damage as valid models of ADHD. Moreover, there is no basis to implicate cerebellar damage or dysfunction in clinical ADHD.

2.2.4. Exposure of animals to environmental toxins

Exposure to environmental toxins including lead and polychlorinated biphenyls (PCBs) might contribute to occasional cases of ADHD [226,240]. Mice chronically exposed to inorganic lead from birth demonstrated markedly increased levels of spontaneous motor activity compared to normal control, that was reduced by treatment with amphetamine and methylphenidate [245,246]. In addition, early exposure of rats to PCB congeners (IUPAC 118, 126 and 153) in utero or through mother's milk has led to impaired visual discrimination and slight motor hyperactivity [123,124]. Rats exposed to PCB-153 as pups also showed behavioral changes indicative of impulsivity such as rapid lever-pressing immediately before a reinforcer became available in an operant task [123,124]. No abnormalities were found in the size, weight, or gross physical development of these rats. Monkeys exposed to lead or PCBs during early development have also shown deficits in both spatial and non-spatial learning tasks, as well as impulsive behaviors in certain operant schedules [210–212].

Mechanisms responsible for behavioral and cognitive abnormalities in animals exposed to PCBs or lead early in life are unknown. In forebrain tissue of mice exposed to lead early in life, a synaptosomal fraction showed increased high-affinity transport of L-tyrosine, and decreased uptake of choline and DA, with increased tissue levels of NE, but not DA or acetylcholine [245,246]. At a symptomatic level, behavioral deficits produced by lead and PCBs are consistent with damage to PFC [154,209], although such effects have not yet been demonstrated.

2.2.5. X-ray damage of hippocampus in rats

Exposure of rat pups to X-irradiation results in a number of behavioral deficits that resemble features of clinical ADHD [66,73,74], even though ionizing radiation is very unlikely to be a significant contributor to human ADHD. Changes produced by early exposure to X-rays include profound hyperactivity and deficits in learning and memory without gross deficits of sensorimotor function [2,3,102,122]. Learning and memory deficits in such early-irradiated rats can be alleviated with d-amphetamine [122]. Behavioral changes in this model may be due to reduced populations of interneurons in forebrain, especially in hippocampus [2,3,102]. A prominent role of hippocampus in this model is also suggested by ADHD-like symptoms such as hyperactivity in rats with focal irradiation of the brain [74].

2.3. Miscellaneous models

2.3.1. Hyposexual male rats

Sexual behavior in rodents is maintained by circulating concentrations of androgenic steroids and levels of their receptors in the preoptic area of brain, and is triggered by external stimuli including the sight, smell, and touch of a receptive female. A high proportion of male rats that fail to copulate with receptive females in a standard environment are hyperactive [142,143]. These rats also show other behavioral features suggestive of ADHD, including overactivity and impulsivity in open field testing, diminished hyperactivity in response to d-amphetamine, and decreased ability to ignore irrelevant information in a conditioned avoidance test [35,142,143].

2.3.2. Animals selected from a general population

Behavioral deficits in the animal models already described are typically induced by a variety of invasive procedures that are unlikely to be encountered in human ADHD patients. Using the five-choice serial reaction time task (5-CSRTT), Puumala and colleagues found that some apparently normal Lister hooded rats tend to show attention deficits and impulsivity [199–201]. The testing paradigm resembles methods commonly used to assess vigilance and sustained attention in human subjects, and requires animals to discriminate a brief visual stimulus presented randomly in one of five locations, and to respond appropriately with a nose-poke to receive reinforcers. In addition to its spontaneous nature, an attractive feature of this model is its focus on sustained attention that is rarely examined in other models. Sustained attention is scored for

accuracy (percent correct responses) and impulsivity (percentage of premature responses). Deficits in the poor-performers were not due to visual impairment, since increasing stimulus intensity or duration did not preferentially affect poor-performers [201]. Also, no relationship was observed between choice-accuracy and latency to collect reinforcers after correct responses, indicating that motivational factors do not underlie the attention deficit or pervasive responses of poor-performers.

Following training of rats in the 5-CSRTT paradigm, tissue from selected brain regions was assayed for monoamines and their metabolites [202]. A measure of metabolic turnover of serotonin (5-HIAA/5-HT ratio) in left frontal cortex correlated inversely with choice-accuracy, whereas DA turnover (DOPAC/DA) in right frontal cortex correlated positively with performance. Premature responses, on the other hand, correlated with 5-HT turnover in right frontal cortex. These findings indicate that DA and 5-HT in frontal cerebral cortex play an important role in the modulation of attention and response control.

The 5-CSRTT behavioral testing procedure not only provides a unique model to simulate attention deficits in ADHD, but has also yielded information on the regulation of sustained attention. Consistent with a prominent role of the central cholinergic system in cognition, choice-accuracy is severely compromised in rats with selective lesions to the nucleus basalis of Meynert [180,181]. Destruction of the mesolimbic DA projection increased response-latency in the 5-CSRTT paradigm, and decreased overall responding, with no apparent effect on choice-accuracy [61], indicating a change in motivation rather than attention. Lesions of NE system, on the other hand, disrupted 5-CSRTT performance only when distracting stimuli were present or target stimuli become temporally unpredictable [60], suggesting that NE transmission serves to direct attention to goal-directed events.

3. Discussion

A summary of animal models of ADHD, with salient similarities to and differences from the clinical disorder, is provided in Table 1.

3.1. Monoaminergic functions in animal models of ADHD

3.1.1. Dopamine

In SHR, behavioral deficits analogous to ADHD symptoms are usually considered to be mediated by an impaired DA reward mechanism that consists mainly of dysregulation of DA release, although changes in postsynaptic responses to DA also have been detected (see Section 2.1.1.). Rats with neonatal 6-OHDA lesions represent another model with decreased DA transmission (see Section 2.2.1). Despite losses of DA that are similar to those in bradykinetic rats with adult 6-OHDA lesions, neonatally lesioned rats display a robust motor hyperactivity that is inhibited by stimulant drugs, but not by selective inhibitors of DA transport. Behavioral deficits in coloboma mutant mice are caused by a mutation of the SNAP-25 gene, with a resulting deficiency in DA transmission (see Section 2.1.3). In striking contrast to SHR, rats with neonatal 6-OHDA lesions, and coloboma mice, the DAT-KO mouse is a model with a completely opposite underlying pathophysiology, namely persistent hyperdopaminergic function (see Section 2.1.2).

The similarity of behavioral and pharmacological profiles of animal models of ADHD based on deficient DA transmission and those with increased DA transmission is paradoxical. As a step toward rationalizing this paradox, we propose that an appropriate, intermediate, level of activity of cerebral catecholamine systems, especially of DA transmission, is essential to maintain normal responses and adaptations to environmental stimuli. Animal models with decreased DA transmission, such as SHR and the neonatally 6-OHDA lesioned rat, and those with increased DA transmission, such as the DAT-KO mouse, represent deviations from an optimal level, albeit in opposite directions. In models with diminished DA transmission, stimulants may be beneficial by enhancing release of DA. In models with excessive DA function, activation of presynaptic D_2-like autoreceptors and the consequent reduction in DA neurotransmission may contribute to the beneficial effects of stimulants.

3.1.2. Norepinephrine

In addition to stimulants that potentiate NE as well as DA, other NE-potentiating agents including tricyclic antidepressants and more selective NE-uptake inhibitors (NRIs), as well as clonidine (a direct postsynaptic α_2 agonist in addition to its α_2-autoreceptor effects that diminish NE-release) are all effective in treating ADHD [32,33,198]. These findings suggest that the central noradrenergic system may be involved in the disorder. Projecting widely throughout the CNS, NE neurons arising in their principal brainstem cell group, the locus coeruleus, are exquisitely sensitive to novelty, suggesting that they are involved in maintaining vigilance and directing attention to relevant stimuli [15,197]. Conversely, reduced central noradrenergic tone may impair these functions [33,197]. Consistent with this hypothesis, selective and extensive depletion of NE in neonatal rat, which can be achieved with 6-OHDA in the presence of a selective DAT-inhibitor [274], leads to motor hyperactivity [207], learning deficits [213], and distractibility in a rodent model that selectively assesses sustained attention [49]. Behavioral effects of drugs that potentiate NE transmission in laboratory models also are consistent with the effectiveness of such agents in the treatment of clinical ADHD.

Contrary to expectations of deficient NE neurotransmission in animal models of ADHD, analyses of the NE

Table 1
Comparison of animal models of ADHD

Model	Similarities to ADHD	Differences from ADHD	Comments
SHR	Hyperactivity in novel environment Motor impulsivity Attention deficit Some response to stimulants	Little association of hypertension with ADHD No sex differences in model Antihypertensives reduce model cognitive deficits and α_2 agonists benefit ADHD (direct central effect?)	Most thoroughly studied ADHD model Need more comparisons of pure hyperactive (WKHA) and hypertensive (WKHT) rats
DAT-KO mouse	Environment-dependent hyperactivity Stimulants reduce hyperactivity Cognitive impairment (radial maze)	Stimulant effects on cognition untested Methylphenidate requires high doses 5-HT agents beneficial in model, not in ADHD Evidence of DAT-*excess* in ADHD	No evidence of DA functional excess in ADHD
Coloboma neutron-irradiated mouse	Spontaneous hyperactivity Low-dose amphetamine reduces hyperactivity	Questionable relationship of ADHD to SNAP-25 gene Not improved by methylphenidate	Specific neural deficits not clear Cognition not well evaluated
NHE rat	Hyperactivity and attention deficits	Circadian motility normal	Requires neuropharmacological evaluation
Acallosal Mouse (I/LnJ)	Excessive arousal in novel environment Impulsive	Stimulants not tested No evidence of callosal dysfunction in ADHD	Needs further characterization
6-OHDA lesioned juvenile rat	Increased nonadaptive locomotor activity No sensory or motor deficits Stimulants attenuate hyperactivity and learning deficits	Lack of sex differences D_4 antagonists reduce hyperactivity	More assessment of attention and impulsivity needed D_4 antagonists need clinical testing
Neonatal anoxic rat	Some hyperactivity Deficits in learning and spatial memory Less active with amphetamine	Hyperactivity short-lived Cognitive effects of stimulants unknown Role of hypoxia in ADHD uncertain	Requires more pharmacological analysis
Cerebellar stunted rat	Hyperactive in novel environment Males more hyperactive	Attention and impulsivity not tested Stimulants untested Cerebellar dysfunction unproved in ADHD	Needs more behavioral comparisons to ADHD Role of cerebellum in ADHD requires assessment
Environmental toxins	Motor hyperactivity common in many species with varied toxins	Stimulant effects have limited testing Relationship of toxins to ADHD not proved	Mediating mechanisms not specified
Hippocampal X-irradiated rat	Hyperactivity present Deficits in memory-based learning Amphetamine improves learning	Stimulant effects on hyperactivity untested Radiation not implicated in ADHD	May model microneuronal hypoplasia or 'minimum brain dysfunction'
Spontaneously inattentive rats	Deficits in sustained attention	Ethylphenidate not beneficial	Pathophysiology undefined
Hyposexual male rat	Spontaneous hyperactivity Deficits in attention Amphetamine reduces hyperactivity	Stimulants untested in ADHD ADHD also in females	ADHD sex-linked in hyperactivity, not to attentional deficits

Abbreviations: DA, dopamine; DAT-KO, dopamine transporter gene knock-out mouse; 5-HT, 5-hydroxytryptamine, serotonin; NHE rat, Naples high-excitability rat; 6-OHDA, 6-hydroxydopamine; SHR, spontaneously hypertensive rat; SNAP-25, synaptosomal associated protein of 25 kDa; WKY, Wistar-Kyoto rat; WKHA, Wistar-Kyoto rat, hyperactive not hypertensive; WKHT, Wistar-Kyoto rat, hypertensive not hyperactive.

system in most ADHD models have indicated normal or increased NE transmission, not decreases. Recent studies of NET-knockout mice also yield little support for a role of excessive NE in ADHD. These mutants did not show altered spontaneous activity or unusual responses to stimulants, although their motor responses to D_2-agonist quinpirole and D_3/D_2-agonist 7-hydroxydipropylaminotetralin (7-OH-DPAT) were increased [300]. The striking disparity between the pathophysiology of animal models of ADHD, and the beneficial effects of NE-potentiating agents in both animal models and in patients with ADHD, call for further consideration of the NE system in both modeling and treatment of ADHD.

3.1.3. Serotonin

Serotonergic neurons display distinctive slow, regular

discharges that change across the sleep–wake cycle and become virtually silent during rapid eye-movement (REM) sleep [132,133]. These neurons coordinate autonomic and neuroendocrine functions with changing motor output, and regulate sensory information processing, as well as exerting motor-facilitating effects at the lateral horn motoneurons [103]. When the 5-HT system is suppressed, such as with orientation to salient stimuli and in REM sleep, motor function is inhibited, and sensory information processing is activated [103,132,133].

Serotonin has been studied closely in few of the animal models of ADHD. In neonatally 6-OHDA lesioned rats, a role of 5-HT transmission is suggested by prominent hyperinnervation of neostriatum with 5-HT fibers and the inhibitory effects of 5-HT-potentiating agents on motor hyperactivity (see Section 2.2.1). In DAT-KO mice, 5-HT also may be critically involved in mediating the behavior-inhibiting effects of stimulants (see Section 2.1.2). Nevertheless, the relevance of these findings to clinical ADHD remains unclear, since fenfluramine and SRIs are not therapeutically effective in ADHD patients [26,198,233].

3.1.4. Acetylcholine and histamine

Maternal smoking is a risk factor for ADHD, and conversely, ADHD is a reported risk factor for early cigarette smoking in children [59,172–174], suggesting that central acetylcholinergic system may be involved in ADHD. A role of cholinergic transmission in ADHD also is generally consistent with evidence of the critical importance of this neurotransmission system in cognitive functions (see Section 2.3.2), and specifically supported by clinical trials finding that treatment with both nicotine and the nicotinic agonist ABT-418 improved attention and arousal in ADHD subjects [62,291].

The central histaminergic system is also implicated in modifying attention and vigilance, possibly through modulating release of DA, NE, and 5-HT [192]. Of note, a new histamine H_3-antagonist GT-2331 is being evaluated as a treatment for ADHD [1,273].

3.1.5. Actions of stimulant drugs

Extensively used to treat patients with ADHD for many years, stimulants such as amphetamine and methylphenidate provide important tests of the validity of animal models of the disorder [56,58,67,187,233]. These drugs are short-acting, with maximal plasma levels and therapeutic actions at 1–3 h, and plasma half-life of 4–8 h in man (much less in rodents) [43,56,58,155,167,169]. Effective daily oral doses for d-amphetamine in children with ADHD are 0.2–0.8 mg/kg, and for dl-methylphenidate, 0.3–1.0 mg/kg [56,58,249]. Methylphenidate can reduce motor hyperactivity in children with ADHD at a dose as low as 0.1 mg/kg, whereas high doses may lead to increased activity and compulsive or stereotyped behaviors and abnormal movements including tics [252,257]. Symptoms of ADHD return within hours after stimulants are discontinued, and within prolonged dosing intervals [17,20,56,233].

There is no evidence of tolerance to clinical benefits of stimulants during prolonged daily use for years, perhaps reflecting their rapid clearance and typical use only during part of each day. However, there is evidence of tachyphylaxis to methylphenidate given in long-acting formulations, with rapidly evolving loss of clinical benefits within hours [107,267]. Clinical use of pulsed-release methylphenidate in rising doses may provide an advantage for children for whom mid-day dosing is a problem, since a single morning dose can afford beneficial behavioral effects throughout the day equivalent to standard twice-daily methylphenidate dosing, while also avoiding loss of response through rapidly evolving pharmacodynamic tolerance [176,177,193,196]. These pharmacological characteristics of stimulants need to be considered in evaluating proposed animal models of ADHD, as well as in optimizing the clinical therapeutics of the disorder.

Responses to stimulants in ADHD patients and normal human subjects vary widely and are not reliably predicted by age, body weight, or blood drug concentration [17,20]. These agents improve attention and reduce activity levels and impulsivity in ADHD patients as well as in normal subjects, probably through enhancing executive functions of the prefrontal cerebral cortex [17,20,204,205]. Based on brain-imaging studies, differences in behavioral responses to methylphenidate correlated with the amount of DA released, suggesting that with an equivalent level of DAT blockade, methylphenidate would produce less release of DA with lower levels of DA neuronal activity [270,284].

A fundamental paradox is that, at low doses, stimulants reduce hyperactivity in several ADHD animal models as well as in clinical ADHD, whereas high doses of same stimulants produce generalized stimulation of nervous system and increase motor activity. Several hypotheses have been offered to resolve this seeming inconsistency [235,236]. They include the idea that stimulants have biphasic effects. Low doses of stimulants reduce the extent to which DA is released with nerve impulses, possibly by activating autoreceptors. This effect reduces activation of postsynaptic D_1 and D_2 receptors, with reduced psychomotor activity [235,236]. At high doses, stimulants increase the release of DA with nerve impulses, elevate the concentrations of extracellular DA, and subsequently increase motor activity by activating postsynaptic DA D_1 and D_2 receptors, and overcoming presynaptic inhibition of DA release [235,236].

3.2. Implications for future studies of ADHD

Most of the experimental models of ADHD considered above rely on behavioral hyperactivity as a primary index to assess effects of clinically proven treatments for ADHD, such as stimulants and tricyclic antidepressants. Much less is known about the effects of these treatments on attention

and impulsivity in these models, though they can provide benefits for these features, as well as for hyperactivity, in clinical ADHD [20,290]. Animal modeling of ADHD is also limited by the still-evolving understanding of the clinical disorder. ADHD has traditionally been perceived as being four to six times more frequent among males than females. However, this view is biased by the prominence of hyperactive and dyssocial behaviors in boys and young men with ADHD [101]. Both brain-imaging studies [55] and psychological testing [237,238] suggest strong similarities between male and female ADHD patients.

There is a great need to bridge the gap between clinical and basic research relevant to ADHD. For example, more than 30 structural and functional neuroimaging studies of the brain in patients diagnosed with ADHD have been reported, using computerized tomography, magnetic resonance imaging, regional cerebral blood flow, glucose metabolism, and radioligand competition assays [104,184,206]. Most of these studies implicate the prefrontal cerebral cortex and its innervation of subcortical regions such as caudate-putamen, nucleus accumbens, and amygdaloid complex, in the pathophysiology of ADHD. Similarities between patients with ADHD and subjects with PFC lesions, especially in right hemisphere, also support the hypothesis that dysfunction of PFC is a critical component of ADHD [7,9,21,27,57,129,168,170, 195,244,292,295]. Studies of the PFC in animal models remain rare, but those that are available, coupled with studies in human subjects, indicate that the right, dorsal PFC may be particularly important for sustaining attention and inhibiting responses to distracting stimuli [54,129,287,292], and that the right orbital PFC regulates behavioral and motor activity [9,265]. These systems should be considered in future studies of animal models of ADHD.

Despite the many advances in developing and analyzing animal models of ADHD, an ideal laboratory model for ADHD has yet to be established. Solanto proposed [254] that valid models of clinical ADHD should include: (a) deficits in measures of attention and impulsivity, and not only motor hyperactivity; (b) amelioration of both cognitive and motor deficits by stimulants and other clinically effective treatments in clinically plausible doses; (c) immediate onset of action and lack of tolerance or sensitization with repeated administration of drugs used to treat ADHD; and (d) effects of therapeutic agents on both DA and NE neurotransmission.

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